REMARKS

ELECTION/RESTRICTION REQUIREMENT

Applicants reiterate their position that the claims as originally filed possess unity of invention as defined in PCT Rule 13. All claims involve or include the presently claimed PARP homolog, which is inventive. The present priority date precedes the publication date of the cited article. Accordingly, all claims should be considered by the present examiner.

INFORMATION DISCLOSURE STATEMENT

Applicants have not yet obtained the proper information concerning Küpper et al., and will provide such as soon as it is available.

SPECIFICATION & DRAWINGS

Applicants have incorporated the sequence identification numbers for the sequences listed in Figure 1 into the specification, in the brief description of the drawings section. This Figure has been amended to meet the draftsperson's requirements. The requested section headings have also been introduced. Two sequences from Figure 1 of the specification have been incorporated into the newly submitted substitute sequence listing. A copy of this substitute sequence listing in computer readable form is attached hereto. The content of the paper copy of the sequence listing and the copy of the sequence listing in computer readable form is the same, and includes no new matter.

CLAIM OBJECTIONS AND REJECTIONS UNDER §101 AND §112

Claim 1 has been amended for consistency. The subject matter of claim 4 has been introduced into claim 1, and claim 4 has been canceled. The examiner objects to the inclusion of additional sequences beyond that elected for examination purposes. Applicants respectfully request that the additional four sequences be included in the examination. The Commissioner of Patents has indicated that a reasonable number of patently distinct nucleotide sequences can be considered in a single application, with MPEP §803.04 extending this to the relevant amino acid sequences, as well (*see Examination of Patent Applications Containing Nucleotide Sequences*, 1192 O.G. 68 (November 19, 1996)).

The "reasonable number" for examination purposes has been set at "up to ten" for independent and distinct sequences, and "those sequences which are patentably indistinct from the selected sequences will also be examined" (MPEP §803.04). Under these guidelines, all five sequences should be considered together, regardless of whether they are ultimately deemed to be "independent and distinct." Applicants consider the structural similarities to be such as to preclude such a finding, and yet the point is not dispositive on this issue. According to USPTO procedures, all of the claimed protein sequences should be examined in the present application.

CLAIM REJECTION UNDER 35 USC §101

Applicants have amended claim 1 to recite an isolated and purified poly(ADP-ribose) polymerase homolog.

CLAIM REJECTIONS UNDER 35 USC §112

Applicants have made amendments to claim 1 which will, hopefully, make the intent of the claim's a) and b) subparts more readily apparent to the examiner. Applicants respectfully submit that one of skill in the art would find the phrase "functional equivalents" to be sufficiently definite. The specification discloses various functions of PARP, and one of skill in the art would recognize other relevant purposes to which PARP equivalents may be set.

The examiner states that there is no disclosure of structure to function/activity relationship in the specification. This is not accurate. Applicants refer the examiner to page 4, line 14 to page 5, line 13, of the specification, which disclose sequences 11-13 to represent a functional NAD^+ binding domain and sequence 14 to represent a leucine zipper motif, likely used in dimer formation. Further, the disclosure starting on page 5, line 15 and extending to page 6, line 13 discusses a number of other part-sequence motifs that are preferably present to ensure PARP functionality. The present claims are additionally drawn to sequences having at least 85% homology with the amino acid sequences specifically claimed and disclosed.

CLAIM REJECTIONS UNDER §102

The claims at issue are rejected under 35 USC §102(a) as being anticipated by Johansson (Genomics 57:442-45 (1999)). The cited reference was accepted for publication in February of 1999 and was published in the May 1, 1999 issue (see attached printout from *ScienceDirect* website). The present application claims priority to

German applications DE 198 25 213.7 and DE 199 08 837.3, filed on June 5, 1998 and March 1, 1999 respectively. Enclosed herewith are certified translations of the priority documents to perfect the claim to priority. Johansson is not prior art.

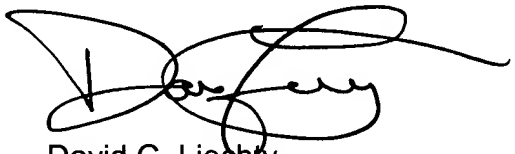
Thibodeau et al. disclose a partial sequence of the rat PARP protein and nucleotide sequences. The disclosed sequence does not anticipate the present claims.

CONCLUSION

In view of the foregoing amendments and remarks, applicants consider that the rejections of record have been obviated and respectfully solicit passage of the application to issue.

Please charge any shortage in fees due in connection with the filing of this paper, including Extension of Time fees to Deposit Account No. 11-0345. Please credit any excess fees to such deposit account.

Respectfully submitted,
KEIL & WEINKAUF



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AMENDMENTS TO THE SPECIFICATION

On line 14 of page 1, please enter the following:

c1 BACKGROUND OF THE INVENTION

On line 8 of page 3, please enter the following:

c2 BRIEF SUMMARY OF THE INVENTION

On line 24 of page 3, please enter the following:

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will now be described in more detail with reference to the appended figures. These show:

c3 In Figure 1 a sequence alignment of human PARP (human PARP1 (SEQ ID NO:35)) and two PARPs preferred according to the invention (human PARP2 (SEQ ID NO:2), human PARP3 (SEQ ID NO:6), murine PARP3 (SEQ ID NO:8)). Sequence agreements between human PARP1 and human PARP2, human PARP3 or murine PARP3 are depicted within frames. The majority sequence (SEQ ID NO:34) is indicated over the alignment. The zinc finger motifs of human PARP1 are located in the sequence sections corresponding to amino acid residues 21 to 56 and 125 to 162;

In Figure 2 Northern blots with various human tissues to illustrate the tissue distribution

of PARP2 and PARP3 molecules according to the invention. Lane 1: brain; lane 2: heart; lane 3: skeletal muscle; lane 4: colon; lane 5: thymus; lane 6: spleen; lane 7: kidney; lane 8: liver; lane 9: intestine; lane 10: placenta; lane 11: lung; lane 12: peripheral blood leukocytes; the respective position of the size standard (kb) is indicated.

In Figure 3 a Northern blot with further various human tissues to illustrate the tissue distribution of the PARP3 molecule according to the invention. Lane 1: heart; lane 2: brain; lane 3: placenta; lane 4: lung; lane 5: liver; lane 6: skeletal muscle; lane 7: kidney; lane 8: pancreas; the respective position of the size standard (kb) is indicated.

c3 In Figure 4 a Western blot with various human tissues to illustrate the tissue distribution of the PARP3 molecule according to the invention at the protein level. Lane 1: heart; lane 2: lung; lane 3: liver; lane 4: spleen; lane 5: kidney; lane 6: colon; lane 7: muscle; lane 8: brain; the respective position of the size standard (kD) is indicated.

In Figure 5 a Western blot with various human tissues to illustrate the tissue distribution of the PARP3 molecule according to the invention. Lane 1: frontal cortex; lane 2: posterior cortex; lane 3: cerebellum; lane 4: hippocampus; lane 5: olfactory bulb; lane 6: striatum; lane 7: thalamus; lane 8: midbrain; lane 9: entorhinal cortex; lane 10: pons; lane 11: medulla; lane 12: spinal cord.

In Figure 6 a diagrammatic representation of the PARP assay (ELISA)

C3

In Figure 7 a diagrammatic representation of the PARP assay (HTRF)

DETAILED DESCRIPTION OF THE INVENTION

Please delete the paragraphs found on page 17, line 26 to page 18, line 23.

Please replace the sequence listing with the newly provided listing appended hereto.

Please amend the drawings as attached hereto.

AMENDMENTS TO THE CLAIMS

~~Please~~ cancel claim 4.

Please amend claim 1 as follows:

1. (currently amended) An isolated and purified ~~A~~ poly(ADP-ribose) polymerase (PARP) homolog ~~and the functional equivalents thereof~~ having an amino acid sequence which ~~has~~

a) has a functional NAD^+ binding domain comprising the sequence motif

$PX_n(S/T)GX_3GKGIYFA$ (SEQ ID NO:11)

in which n is an integral value from 1 to 5, and the X radicals are, independently of one another, any amino acid;

and

b) lacks a ~~no~~ zinc finger sequence motif of the general formula

$CX_2CX_mHX_2C$ ~~$CX_2CX_MHX_2C$~~ (SEQ ID NO:30)

in which

m is an integral value of 28 or 30, and the X radicals are, independently of one another, any amino acid;

~~and wherein the functional NAD^+ binding domain comprises the sequence motif $PX_n(S/T)GX_3GKGIYFA$ (SEQ ID NO:11) in which n is an integral value from 1 to 5, and the X radicals are, independently of one another, any amino acid~~ said PARP homolog being selected from the group consisting of human PARP2 (SEQ ID NO: 2), human PARP3 type 1 (SEQ ID NO:4), human PARP3 type 2 (SEQ ID

C5

NO:6), murine PARP long form (SEQ ID NO:8), murine PARP short form (SEQ ID NO:10), and functional equivalents thereof which are at least 85% homologous.

COMPLETE LISTING OF ALL CLAIMS IN THE APPLICATION

1. (currently amended) An isolated and purified poly(ADP-ribose) polymerase (PARP) homolog having an amino acid sequence which

a) has a functional NAD^+ binding domain comprising the sequence motif
$PX_n(S/T)GX_3GKGIYFA$ (SEQ ID NO:11)
in which n is an integral value from 1 to 5, and the X radicals are, independently of one another, any amino acid;

and

b) lacks a zinc finger sequence motif of the general formula
$CX_2CX_mHX_2C$ (SEQ ID NO:30)
in which
m is an integral value of 28 or 30, and the X radicals are, independently of one another, any amino acid;

said PARP homolog being selected from the group consisting of human PARP2 (SEQ ID NO: 2), human PARP3 type 1 (SEQ ID NO:4), human PARP3 type 2 (SEQ ID NO:6), murine PARP long form (SEQ ID NO:8), murine PARP short form (SEQ ID NO:10), and functional equivalents thereof which are at least 85% homologous.

2. (previously amended) A PARP homolog as claimed in claim 1, wherein the functional NAD^+ binding domain comprises one of the following general sequence motifs:

$(S/T)XGLR(I/V)XPX_n(S/T)GX_3GKGIYFA$ (SEQ ID NO:12) or
$LLWHG(S/T)X_7IL(S/T)XGLR(I/V)XPX_n(S/T)GX_3GKGIYFAX_3SKSAXY$ (SEQ ID NO:13)

in which
n is an integral value from 1 to 5, and the X radicals are, independently of one another, any amino acid.

3. (previously amended) A PARP homolog as claimed in claim 1, comprising at least another one of the following part-sequence motifs:

$LX_9NX_2YX_2QLLX(D/E)X_{10/11}WGRVG$ (SEQ ID NO: 15),
$AX_3FXKX_4KTXNXWX_5FX_3PXK$ (SEQ ID NO:16),
$QXL(I/L)X_2IX_9MX_{10}PLGKLX_3QIX_6L$ (SEQ ID NO:17),
$FYTXIPHXFGX_3PP$ (SEQ ID NO:18); and
$KX_3LX_2LXDIEXAX_2L$ (SEQ ID NO:19),

in which the X radicals are, independently of one another, any amino acid.

4. (canceled)

5. (previously amended) A binding partner for PARP homologs as claimed in claim 1, selected from
   a) antibodies and fragments thereof,
   b) protein-like compounds which interact with a part-sequence of the protein, and
   c) low molecular weight effectors which modulate the catalytic PARP activity or another biological function of a PARP molecule.

6. (previously amended) A nucleic acid comprising
   a) a nucleotide sequence coding for at least one PARP homolog as claimed in claim 1, or the complementary nucleotide sequence thereof;
   b) a nucleotide sequence which hybridizes with a sequence as specified in a) under stringent conditions; or
   c) nucleotide sequences which are derived from the nucleotide sequences defined in a) and b) through the degeneracy of the genetic code.

7. (original) A nucleic acid as claimed in claim 6, comprising

   a) nucleotides +3 to +1715 shown in SEQ ID NO:1;
   b) nucleotides +242 to +1843 shown in SEQ ID NO:3;
   c) nucleotides +221 to +1843 shown in SEQ ID NO:5;
   d) nucleotides +112 to +1710 shown in SEQ ID NO:7; or
   e) nucleotides +1 to +1584 shown in SEQ ID NO:9.

8. (previously amended) An expression cassette comprising, under the genetic control of at least one regulatory nucleotide sequence, at least one nucleotide sequence as claimed in claim 6.

9. (original) A recombinant vector comprising at least one expression cassette as claimed in claim 8.

10. (original) A recombinant microorganism comprising at least one recombinant vector as claimed in claim 9.

11. (original) A transgenic mammal comprising a vector as claimed in claim 9.

12. (previously amended) A PARP-deficient mammal or PARP-deficient eukaryotic cell, in which functional expression of at least one gene which codes for a PARP homolog as claimed in claim 1 is inhibited.

13. (previously amended) An in vitro detection method for PARP inhibitors, which comprises

    a) incubating an unsupported or supported polyADP-ribosylatable target with a reaction mixture comprising
       a1) a PARP homolog as claimed in claim 1,
       a2) a PARP activator; and
       a3) a PARP inhibitor or an analyte in which at least one PARP inhibitor is suspected;
    b) carrying out the polyADP ribosylation reaction; and
    c) determining the polyADP ribosylation of the target qualitatively or quantitatively.

14. (original) A method as claimed in claim 13, wherein the PARP homolog is preincubated with the PARP activator and the PARP inhibitor or an analyte in which at least one PARP inhibitor is suspected, before the polyADP ribosylation reaction is carried out.

15. (original) A method as claimed in claim 13, wherein the polyADP-ribosylatable target is a histone protein.

16. (previously amended) A method as claimed claim 13, wherein the PARP activator is activated DNA.

17. (previously amended) A method as claimed in claim 13, wherein the polyADP ribosylation reaction is started by adding NAD^+.

18. (previously amended) A method as claimed in claim 13, wherein the polyADP ribosylation of the supported target is determined using anti-poly(ADP-ribose) antibodies.

19. (previously amended) A method as claimed in claim 13, wherein the unsupported target is labeled with an acceptor fluorophore.

20. (original) A method as claimed in claim 19, wherein the polyADP ribosylation of the unsupported target is determined using anti-poly(ADP-ribose) antibody which is labeled with a donor fluorophore which is able to transfer energy to the acceptor fluorophore.

21. (original) A method as claimed in claim 19, wherein the target is biotinylated histone, and the acceptor fluorophore is coupled thereto via avidin or streptavidin.

22. (previously amended) A method as claimed in claim 20, wherein the anti-poly(ADP-ribose) antibody carries a europium cryptate as donor fluorophore.

23. (previously amended) An in vitro screening method for binding partners for a PARP molecule, which comprises
    a1) immobilizing at least one PARP homolog as claimed in claim 1 on a support;
    b1) contacting the immobilized PARP homolog with an analyte in which at least one binding partner is suspected; and
    c1) determining, where appropriate after an incubation period, analyte constituents bound to the immobilized PARP homolog;

    or

    a2) immobilizing on a support an analyte which comprises at least one possible binding partner for a PARP molecule;
    b2) contacting the immobilized analyte with at least one PARP homolog as claimed in claim 1 for which a binding partner is sought; and
    c2) examining the immobilized analyte, where appropriate after an incubation period, for binding of the PARP homolog.

24. (previously amended) A method for the qualitative or quantitative determination of nucleic acids encoding a PARP homolog as claimed in claim 1, which comprises
    a) incubating a biological sample with a defined amount of an exogenous nucleic acid, hybridizing under stringent conditions, determining the hybridizing nucleic acids and, where appropriate, comparing with a standard; or

    b) incubating a biological sample with a pair of oligonucleotide primers with specificity for a PARP homolog-encoding nucleic acid, amplifying the nucleic acid, determining the amplification product and, where appropriate, comparing with a standard.

25. (previously amended) A method for the qualitative or quantitative determination of a PARP homolog as claimed in claim 1, which comprises
    a) incubating a biological sample with a binding partner specific for a PARP homolog,
    b) detecting the binding partner/PARP complex and, where appropriate,
    c) comparing the result with a standard.

26. (original) A method as claimed in claim 25, wherein the binding partner is an antibody or a binding fragment thereof, which carries a detectable label where

appropriate.

27. (original) A method as claimed in claim 24 for diagnosing energy deficit-mediated illnesses.

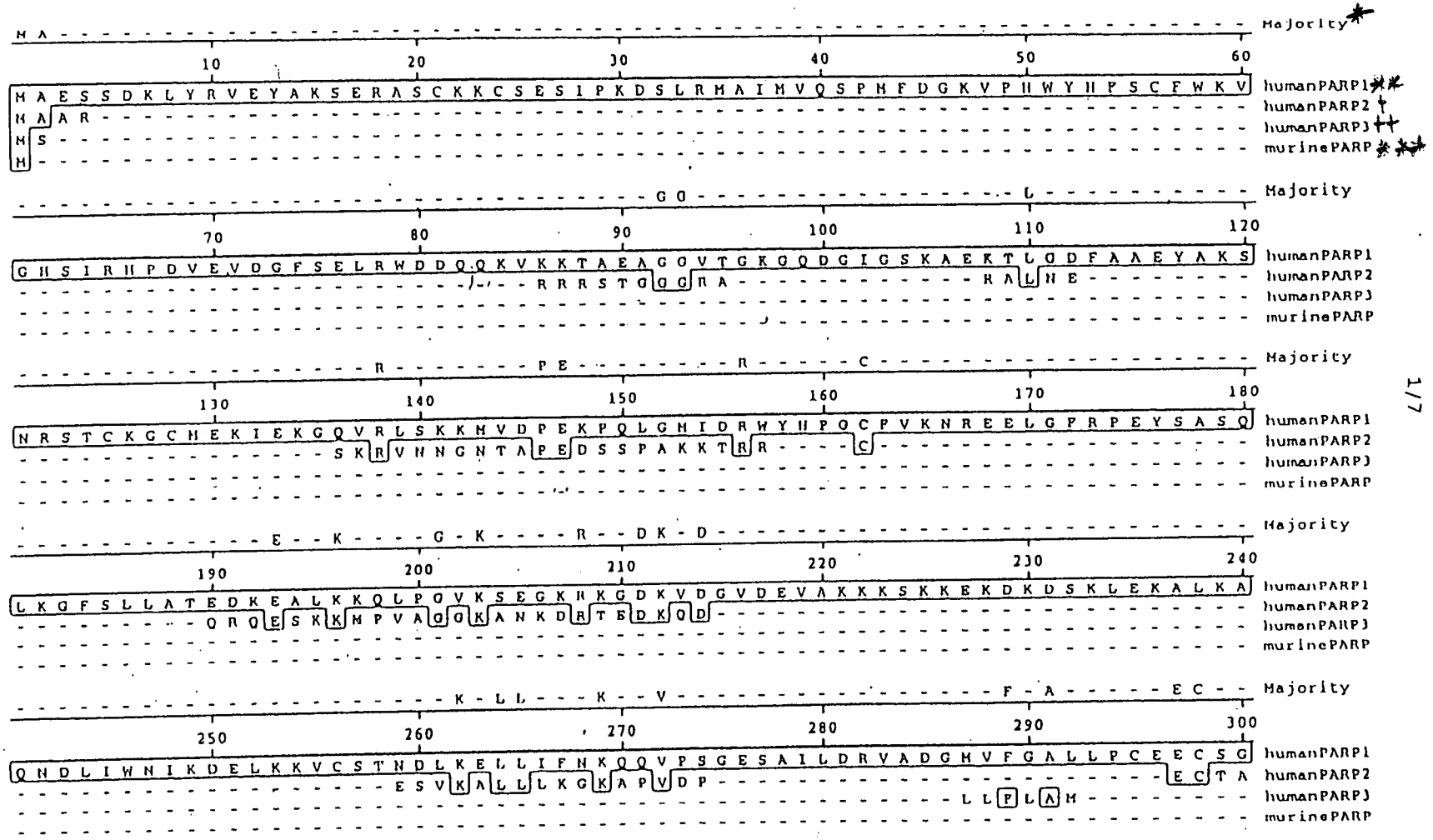
28. (previously amended) A method for determining the efficacy of PARP effectors, which comprises
    a) incubating a PARP homolog as claimed in claim 1 with an analyte which comprises an effector of a physiological or pathological PARP activity; removing the effector again where appropriate; and
    b) determining the activity of the PARP homolog, where appropriate after adding substrates or cosubstrates.

29. (previously amended) A gene therapy composition, which comprises in a vehicle acceptable for gene therapy a nucleic acid construct which
    a) comprises an antisense nucleic acid against a coding nucleic acid as claimed in claim 6; or
    b) a ribozyme against a nucleic acid as claimed in claim 6; or
    c) codes for a specific PARP inhibitor.

30. (previously amended) A pharmaceutical composition comprising, in a pharmaceutically acceptable vehicle, at least one PARP protein as claimed in claim 1, at least one PARP binding partner or at least one coding nucleotide sequence.

31. (original) The use of low molecular weight PARP binding partners as claimed in claim 5 for the diagnosis or therapy of pathological states in the development and/or progress of which at least one PARP protein, or a polypeptide derived therefrom, is involved.

32. (original) The use of low molecular weight PARP binding partners as claimed in claim 5 for the diagnosis or therapy of pathological states mediated by an energy deficit.



~~Fig. 1(1)~~
Fig. 1A

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                         310       320       330       340       350       360
         ---------YC-G-------------APKRKXWV-------------------------Q  Majority
301      QLVPKSDAYYCTGDVTAWTKCMVKTQTPNRKEWVTPKEFREISYLKKLKVKKQDRIFPPE  humanPARP1
88       KVG--KAHVYCEGN----------------------------------------------  humanPARP2
9        --------------------------APKPKPWV-------------------------Q  humanPARP3
2        --------------------------APKRKASV-------------------------Q  murinePARP

                         370       380       390       400       410       420
         TEGS--------------------------------------------------------  Majority
361      TSASVAATPPPSTASAPAAVNSSASADKPLSNMKILTLGKLSRNKDEVKAMIEKLGGKLT  humanPARP1
100      ------------------------------------------------------------  humanPARP2
18       TEGP--------------------------------------------------------  humanPARP3
11       TEGS--------------------------------------------------------  murinePARP

                         430       440       450       460       470       480
         ----------------EKKKXRQXXXEEDXPRSTAEAL----------------------  Majority
421      GTANKASLCISTKKEVEKMNKKMEEVKEANIRVVSEDFLQDVSASTKSLQELFLAHILSP  humanPARP1
100      ------------------------------------------------------------  humanPARP2
22       ----------------EKKKGRQAORENEDPFRSTAEAL---------------------  humanPARP3
15       ------------------KKQRQOTEEEDSFRSTAEAL----------------------  murinePARP

                         490       500       510       520       530       540
         -----KAXPAEXRXIRVDPXCPLSXNPGXQVXED--------------------------  Majority
481      WGAEVKAEPVEVVAPRGKSGAALSKKSKGQVKEEGINKSEKRMKLTLKGGAAVDPDSGLE  humanPARP1
100      ------------------------------------------------------------  humanPARP2
44       -----KAIPAEKRIIRVDPTCPLSSNPGTQVYED--------------------------  humanPARP3
35       -----RAAPADNRVIRVDPSCPFSRNPGIQVHED--------------------------  murinePARP

                         550       560       570       580       590       600
         -----------VYDCTLNQTNIXNNNNKFYIIQLLEDDX-RFFXCWNRWGRVGE-VGQSK  Majority
541      HSAHVLEKGGKVFSATLGLVDIVKGTNSYYKLQLLEDDKENRYWIFRSWGRVGTVIGSNK  humanPARP1
100      ----------DVYDVMLNQTNLQPNNNKYYLIQLLEDDAQRNFSVWMRWGRVGKM-GQHS  humanPARP2
73       ------------YNCTLNQTNIENNNNKFYIIQLLQDSN-RPFTCWNRWGRVGE-VGQSK  humanPARP3
64       ------------YDCTLNQTNIGNNNNKFYIIQLLEEQS-RPF-CWNRWGRVGE-VGQSK  murinePARP
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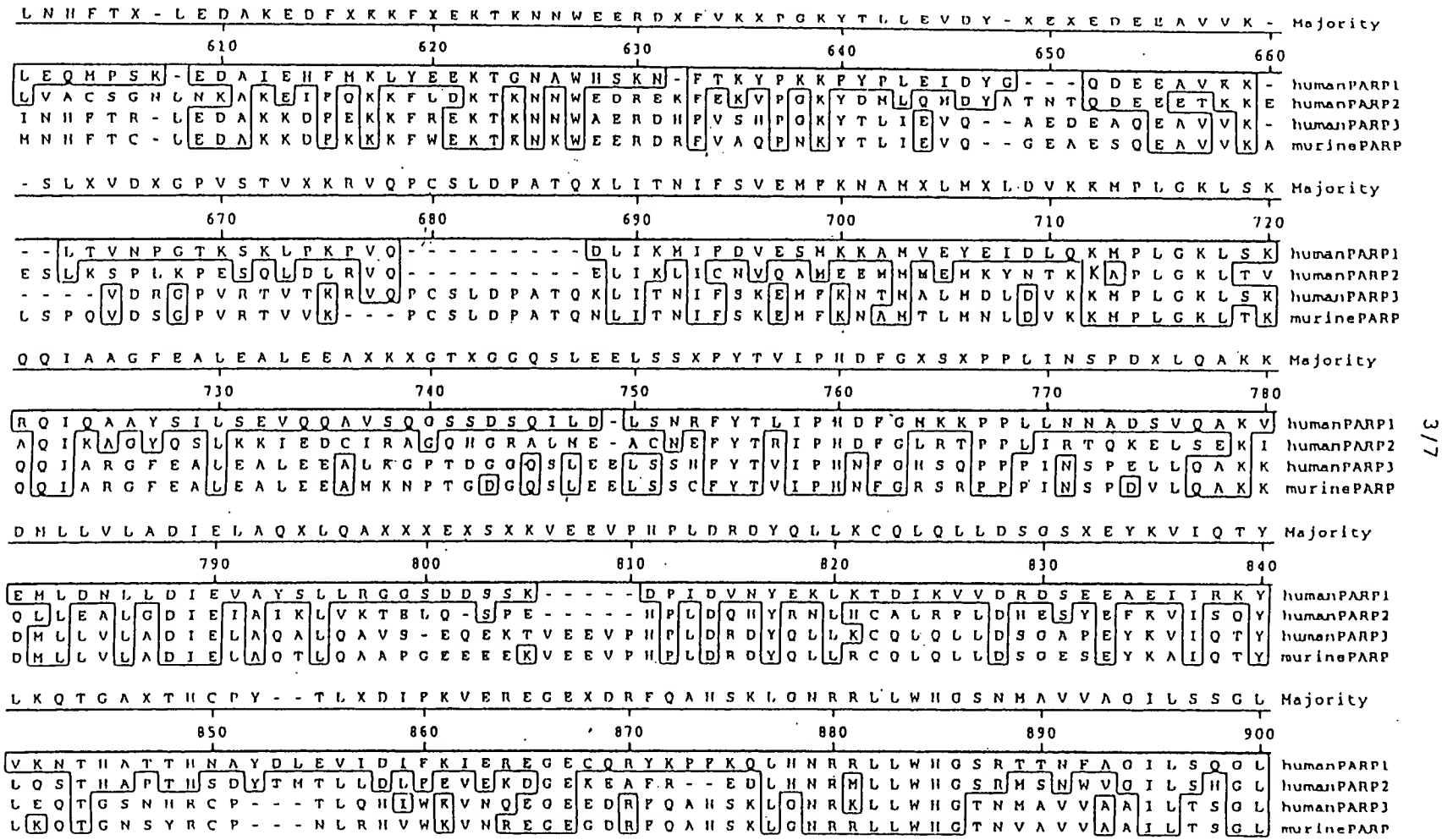
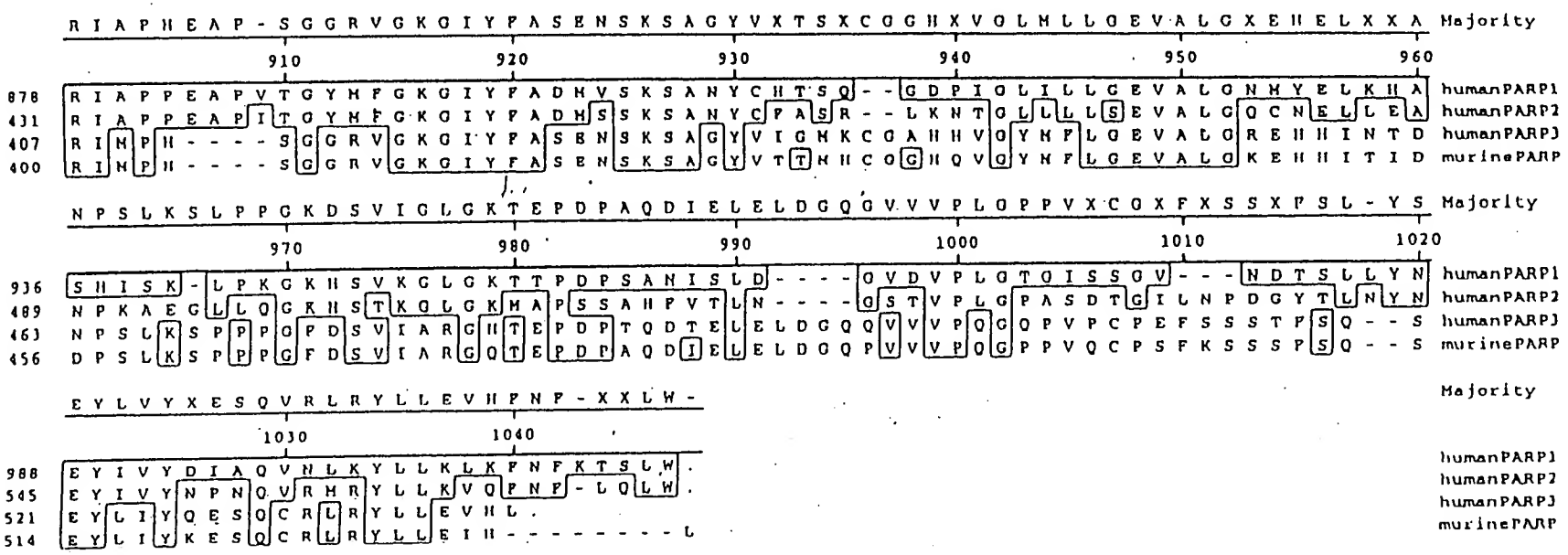
~~Fig. 1(2)~~

Fig. 1B



~~Fig. 1(3)~~

Fig. 1C



~~Fig. 1(4)~~

Fig. 1D